PHENYLTHIOMETHYL-6-HYDROXY-2,3-DIHYDROBENZO-PYRAN AND ANALOGS THEREOF USEFUL AS ANTI-INFLAMMATORY AGENTS

BACKGROUND OF THE INVENTION

The present invention relates to novel substituted 6-hydroxy-2,3-dihydrobenzopyran and analogs thereof useful as anti-inflammatory agents.

It has been observed that the novel compounds of this invention are active in vitro in both the peritoneal macrophage assay and the polymorphonuclear leukocyte assay for general anti-inflammatory activity. Specifically, they are found to be active in vivo in the mouse ear assay for topical anti-inflammatory agents. Furthermore, these compounds tend to be inactivated in vivo after deeper and longer penetration into the body system and are therefore devoid of any significant adverse side effects normally associated with systemic activity.

Recent studies demonstrated that macrophages participate in the development and progression of chronic inflammatory diseases such as rheumatoid arthritis. During the progression of inflammatory conditions, there is generally an appearance and/or presence of macrophages and lymphocytes, especially macrophages and polymorphonuclear leukocytes. Macrophages are known to secrete various products in response to inflammatory stimuli. For example:

(1) Neutral proteases—the destructive peptide bond cleaving enzymes which have been shown to be directly involved in rheumatoid cartilage destruction; and

(2) Prostaglandins (PG) (e.g., E_2 and I_2 by mouse peritoneal macrophages) and other arachidonic acid derivatives derived from both the cyclooxygenase and the lipoxygenase pathways.

These arachidonic acid oxygenation products have been identified as the critical mediators of various acute inflammatory conditions.

Accordingly, pharmacological agents which are capable of inhibiting the formation or the release of a mediator and thereby interfere with the function of macrophages or polymorphonuclear leukocytes may also be effective anti-inflammatory agents. For example, nonsteroidal anti-inflammatory drugs such as indomethacin and clinoril are known cyclooxygenase inhibitors. Through their ability to inhibit the formation of prostaglandins, they have been used for rheumatoid arthritis and osteoarthritis. Other inflammatory diseases such as emphysema, bronchial inflammation, acute respiratory distress syndrome, spondylitis, lupus, gout, and psoriasis may also be treated with these pharmacological agents.

Regarding the topical mouse ear assay, it has been previously established that classical nonsteroidal anti-inflammatory agents such as indomethacin and steroidal anti-inflammatory agents such as dexamethasone are active in this assay.

Another object of this invention is to provide appropriate processes for the preparation of the subject novel compounds.

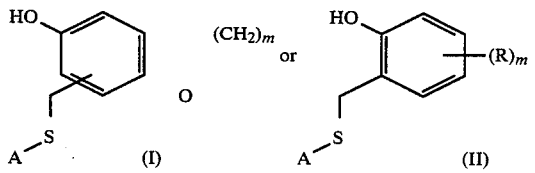
Still a further object of the present invention is to provide a pharmaceutically acceptable composition containing an effective amount of the active compound for the treatment of various inflammatory conditions.

Finally, it is the ultimate object of this invention to develop a method of treating inflammation via the administration of a therapeutically effective amount of the novel compounds or pharmaceutically acceptable composition thereof to a mammalian species in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

A. Scope of the Invention

This invention relates to novel compounds of formula (I) and (II)



or a pharmaceutically acceptable salt thereof, wherein R is

(a) hydroxyloweralkyl especially C_{1-6} hydroxyalkyl such as $-CH_2OH$, $-CH_2CH_2OH$ or

(b) lower alkanoyl;

(c) CN;

(d) halo;

(e) mercaptoloweralkyl especially mercapto C_{1-6} alkyl such as $-CH_2SR^2$ where R^2 represents H or loweralkyl,

(f) loweralkylthio especially C_{1-6}alkylthio such as $-SCH_3$;

(g) lowerhaloalkyl;

(h) $-COOR^2$;

(i) hydroxycarbonylloweralkyl especially hydroxycarbonyl-C_{1-6} alkyl such as $-CH_2COOH$;

(j) loweralkoxycarbonylloweralkyl especially C_{1-6} alkoxycarbonyl C_{1-6} alkyl such as $-CH_2COO$ t-Bu;

(k) halololoweralkanoyl especially halo C_{1-6} alkanoyl such as trifluoroacetyl;

(l) loweralkoxy especially C_{1-6} alkoxy such as methoxy, ethoxy and propoxy, with the proviso that R cannot be loweralkoxy when A is phenyl; or

(m) loweralkanoyloxyloweralkyl such as $-CH_2OCOCH_3$;

m is an integer ranging from 1 to 4;

A is

(a) phenyl substituted with $(R^1)_q$ wherein when there are more than one R^1 (i.e., $q>1$), they can be the same or different from each other and is

(1) hydrogen;

(2) halo especially fluorb, chloro or bromo;

(3) loweralkoxy especially C_{1-6} alkoxy, e.g., methoxy, ethoxy, isopropoxy, t-butoxy or cyclohexyloxy, or $-OCH_2O-$;

(4) lower alkylthio especially C_{1-6} alkylthio, or C_{1-6} haloalkylthio e.g., methylthio, ethylthio, trifluoromethylthio or cyclohexylthio;

(5) lower alkyl sulfinyl especially C_{1-6} alkyl sulfinyl, e.g., methyl sulfinyl, i-propyl sulfinyl, and cyclopentyl sulfinyl;

(6) lower alkyl sulfonyl especially C_{1-6} alkyl sulfonyl such as methyl sulfonyl, ethyl sulfonyl and n-butyl sulfonyl;